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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,245	07/22/2003	Shuichi Mizuno	3831.08	9296

23308 7590 02/19/2009

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EXAMINER	
NAFF, DAVID M	
ART UNIT	PAPER NUMBER
1657	
MAIL DATE	DELIVERY MODE
02/19/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/625,245	MIZUNO ET AL.	
	Examiner	Art Unit	
	David M. Naff	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-95* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/1/08 has been entered.

An amendment of 12/1/08 canceled all claims and added new claims 84-95.

Claims examined on the merits ae 84-95 which are all claims in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 84-95 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Support is not found in the specification for at least 50% more S-GAG and at least 49 % more DNA than a control as required in the last two lines of claim 84. Support is not found in lines 6-12 of paragraph 0228 and Table 2.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 84-95 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 83 is confusing and unclear by being product-by-process by defining the claimed implantable construct in terms of process steps and conditions of how the construct is produced, and not setting forth clear, distinct and positive process steps in the order they are carried out such that there is a clear relationship between the steps, and each step has clear antecedent basis in a previous step. A product-by-process claim must set forth process steps as would be recited in a process of making the product. See MPEP 2113 and 2173.05(P) as to the proper form of a product-by-process claim.

The amendment urges the new claims are not product-by-process. However, claim 84 is clearly requiring process limitations for producing the construct.

Claims 84 and 85 are unclear as to how constant hydrostatic pressure can have a frequency as required of "Hz".

Claims 84 and 91 are unclear as to structure that is a "tissue processor", and in claim 91 structure that is a "Tissue Engineering Support System". Structure that is within and not within the scope of these limitations is uncertain.

In claim 84, requiring synthesizing extracellular matrix, S-GAG and DNA is confusing as to whether these are separate components or are components that form the extracellular matrix formed. The claim is unclear whether the components are synthesized inside the chondrocytes or exterior to the chondrocytes.

In the last line, claim 84 is unclear how the control of non-activated chondrocytes is produced.

In claim 87, "honeycomb-like is uncertain as to meaning and scope. Being like a honeycomb is relative and subjective.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 84-95 are rejected under 35 U.S.C. 102(a) as being anticipated by Smith et al (6,528,052).

The claims are drawn to a hyaline cartilage construct comprising a collagenous porous support matrix having pores between 100 and 300 μm seeded with chondrocytes activated in a tissue processor under conditions of cyclic or constant hydrostatic pressure so the chondrocytes synthesize an extracellular matrix, S-GAG and DNA, and at least 50% more of S-GAG and at least 49% more of DNA is synthesized than a control. Activation involves applying a cyclic or constant hydrostatic pressure from about 0.5 to 5 MPa above atmospheric pressure at a frequency of from about 0.01 to 2 Hz for about one hour to 30 days followed by a resting period from about one day to sixty days, under perfusion with a perfusion medium at a flow rate from about 1 to 500 uL per minute under an oxygen concentration of 1-20%.

Smith et al disclose repair and regeneration of cartilage by a process that involves *in vivo*, *ex vivo* or *in vitro* treatment of cartilage or cartilage cells (chondrocytes) in a support such as a scaffold or collagen matrix (col 6, lines 14-16) by using a loading regiment involving conditions of intermittent application of periods of hydrostatic pressure followed by periods of recovery *in situ* (col 4, lines 25-31, and col 7, line 30 to col 8, line 8). The recovery period can be at atmospheric or low constant pressure (col 7, lines 48-50). *In* vitro treatment is performed

by obtaining cartilage cells from cartilage, and applying the loading regiment conditions while culturing the cartilage cells in suspension within a scaffold/support, and implanting the resultant tissue or cells into a patient (col 9, lines 23-30, and col 11, lines 5-9). Articular chondrocytes (col 16, line 65) are isolated from cartilage using enzyme digestion (col 17, line 4). The chondrocytes can be autologous or not autologous (col 9, line 33). Articular cartilage can be regenerated and repaired (col 1, lines 41-43).

A cartilage construct produced by the process of Smith et al is the same the construct presently claimed for implantation into a cartilage lesion or defect. No difference is seen in the presently claimed process from the process of Smith et al that would result in a materially different construct. The process of Smith et al will inherently produce a construct containing extracellular matrix, S-GAG and DNA as claimed

The presently claimed invention is not disclosed in parent application 10/104,677, and the parent application cannot be relied on for a priority date earlier than the filing date the present application.

Response to Arguments

The amendment urges that Smith et al disclose conditions required by the claims for producing hyaline cartilage. However, conditions disclose by Smith et al are sufficiently similar to those claimed such that the resultant cartilage will be the same as produced by conditions required by the present claims. Smith et al isolate chondrocytes that are inherently mature (Example 1) since they are adult articular chondrocytes from radiocarpal joints (col 16, lines 65-67). These chondrocytes are inherently non-dividing and inactive, and inherently result in hyaline cartilage being produced. The present specification discloses no source of cartilage for isolating chondrocytes other than disclosed by Smith et al. Applying hydrostatic pressure at a frequency disclosed by Smith et al inherently rejuvenates the isolated chondrocytes so the

chondrocytes proliferate and produce DNA, extracellular matrix and S-GAG as evidenced by Smith et al disclosing (col 11, lines 7-10) that the hydrostatic pressure increases metabolic activity and decreases expression of destructive enzymes of chondrocytes. The process of Smith et al will inherently produces a percent of S-GAG and DNA compared to a control as claimed.

The response points to process conditions of the present claims. However, there is inadequate evidence to support that any process conditions of the claims that may not be disclosed by Smith et al result in a construct materially different than results from the process of Smith et al.

Claim Rejections - 35 USC § 103

Claims 84-95 are rejected under 35 U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052) in view of Lee et al (6,306,169) and Burg (6,991,652), and if necessary in further view of Atkinson et al (6,511,958).

The invention and Smith et al are described above.

Lee et al disclose producing an implant containing cells such as chondrocytes (col 7, line 8) by isolating the cells from tissue, proliferating the cells in a medium containing serum to obtain a sufficient number of cells, and seeding the cells in a construct (col 7, lines 13-17) such as a collagen sponge (col 12, line 17). A collagen sponge can be infiltrated with an alginate or agarose solution containing the cells, and the alginate or agarose gelled within the sponge (col 13, lines 11-25). This procedure produces a construct having mechanical function that resembles that processed by tissue to be repaired (col 4, lines 28-37).

Burg discloses forming a hydrogel-cell composition for use in forming new tissue such as cartilage. Before the cell are incorporated in a construct, the cells can be expanded in number by culturing in vitro in a medium containing serum (col 7, lines 20-29). Temperature-

dependent hydrogels can be used (paragraph bridging cols 5 and 6). The hydrogels have reverse gelation properties, and are liquids at or below room temperature, and gel when warmed to higher temperatures, e.g. body temperature.

When incorporating chondrocytes from cartilage into a scaffold for treatment as disclosed by Smith et al, it would have been obvious to expand the number of cells by *in vitro* culturing in a culture medium prior to incorporating the cells in the scaffold as suggested by Lee et al and Burg expanding the number of cells before incorporating the cells in a scaffold for implanting. The resultant construct will be a cartilage construct as presently claimed. Smith et al disclose using a hydrostatic pressure and frequency of applying the pressure that are the same or substantially the same as used in the present claims. Perfusion with a medium as claimed during treatment with hydrostatic pressure would have been obvious to provide nutrients for the cells to maintain the cells active for growth. The conditions of dependent claims are suggested by conditions used by the references. Air contains slightly above 20% oxygen and using slightly less than 20% oxygen would have been an obvious variation that would not be expected to produce a difference in result. Smith et al disclose 7.5% carbon dioxide (col 17, line 10), and using 5% as in claim 94 is an obvious variation that would not be expected to produce a difference in result. Atkinson et al further disclose repairing cartilage lesions, and if needed would have further suggested conditions that can be used.

Response to Arguments

The response urges that Smith et al and the other references do not suggest process conditions of the present claims. However, for reasons set forth, conditions that are the same or substantially the same are suggested by Smith et al will inherently provide a construct materially the same as produced by conditons of the present claims. The amendment urges that the references fail to disclose the importance of conditions claimed. However, evidence has not

been presented establishing the claimed conditions produce a materially different cartilage construct than produced when carrying out Smith et al as set forth above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David M. Naff whose telephone number is 571-272-0920. The examiner can normally be reached on Monday-Friday 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on 571-272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David M. Naff/
Primary Examiner, Art Unit 1657

DMN
2/17/09